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Early pediatric formulation development with new chemical entities: Opportunities of e-tongue besides human taste assessment

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ABSTRACT

The palatability of a pediatric drug formulation is one of the key prerequisites for therapeutic success. Liquid formulations are often chosen for pediatric drug products, and they require special attention regarding their taste, as they have direct contact to the taste buds and a relatively long residence time in the oral cavity. For ethical reasons, the role of electronic tongues in the development of oral drug formulations with new chemical entities (NCEs) for pediatric use is growing, however, little is known about the strategies how this instrumental taste assessment can be performed.

The present study illustrates two possibilities to combine in-vitro and in-vivo data for the characterization of the palatability of the new drug candidates CSE3104 and CSE3165. As a first step, the implementation and suitability of electronic tongue measurements has been demonstrated by comparison of in-vivo and in-vitro data. In alignment with the taste assessment results during a single-center, double-blinded, randomized, placebo-controlled, single ascending dose (SAD) study in healthy subjects, the bitter taste perception of CSE3104 was assessed with e-tongue measurements. Moreover, the sensor response pattern showed comparable results of the e-tongue measurements to the human taste study of CSE3165: With increasing concentration, the bitterness values were increased. In addition, the human taste pattern showed increasing values for sourness due to higher volumes of the citric acid buffer. Results of the hedonic descriptor “unpleasant” within the human taste assessments could be related to bitterness in the instrumental taste assessment.

For the second step in electronic tongue guided formulation development two possibilities are depicted in the article focusing on the effect of different excipients on the formulation on the one hand and on the assessment and comparison of two drug formulations on the other hand.

Based on these results, the low number of healthy volunteers for the taste assessment in a Phase 1 study led to a meaningful interpretation, by applying in addition the electronic tongue. Using this instrumental approach led to reproducible data versus the human taste assessment, without ethical concerns, and with a reduction in time and costs.

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1. Introduction

In the pharmaceutical development of new chemical entities an early planning for a pediatric development is necessary. A pediatric investigation plan (PIP) has to be submitted to the EMA after the Phase I results have been issued according to Regulation (EC) No 1901/2006 and Regulation (EC) No 1902/2006 (Regulation (EC), 2006a, b). A strategy for selecting a suitable pediatric formulation needs to be set up at a very early time point, at which only predictive dose information are available and the toxicological assessment is limited. Ideally, the characterization of the new compound in support of the pediatric formulation strategy can be even covered already in the preformulation phase. The selection of

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an age appropriate formulation depends strongly on the targeted age groups in children. Beside the palatability and swallowability of the formulation the dosing flexibility has high importance since in the early stages of clinical development the predicted final therapeutic doses underlie high uncertainties. Highest possible dosing flexibility can be provided with liquid dosage forms (Liu et al., 2015). On the other hand, liquid forms involve an increased risk of lacking acceptance potentially caused by taste issues that cannot be fully overcome by use of flavors and sweeteners (Sohi et al., 2004; Wagh and Ghadlinge, 2009). Increasingly, highly active compounds are developed nowadays and with the lack of knowledge about the toxicological profile in the early stages of drug development, preclinical tools for the assessment of the taste have become more relevant during pharmaceutical development (Mohamed-Ahmed et al., 2016). The electronic tongue represents a tool which allows an early taste assessment in Phase 0, prior to elaborating the pediatric formulation strategy (Legin et al., 2004). Once the Phase I trials in healthy volunteers start, the opportunity is provided to integrate taste assessment questionnaires into the studies. The obtained early taste information can be used to confirm or adjust the formulation strategy (Cram et al., 2009). During the safety evaluation of a new compound in Phase 1, human studies with the solely purpose of a taste evaluation by a (trained) panel are not justified, particularly for highly potent compounds. Different oral liquid formulations can be tested in-vitro by using an electronic tongue with respect to their comparability and similarity in taste, particularly if for one of the formulations the taste in humans has been already assessed. However, for a new compound, for which the concentration dependent taste perception in humans is not known, the sensor responses of the electronic tongue can only give a certain idea of the taste pattern when analyzed with sensors of global selectivity (Kobayashi and Ikezaki, 2013; Toko, 1996). The electronic tongue provides the opportunity to obtain early signs for taste issues with clinical formulations (Legin et al., 2004; Zheng and Keeney, 2006; Woertz et al., 2011; Anand et al., 2007). For pharmaceutical small molecules the most frequent taste issues relate to bitterness.

In this paper, assessments for two new drug candidates with the electronic tongue are presented using simple oral solutions, which are typically used in Phase I dose escalation studies at different doses and drug concentrations. The drug candidates, CSE3104 and CSE3165, have been selected for the clinical development of the treatment of a pediatric indication, for which drug solutions were required as age appropriate formulation providing high dosing flexibility. Based on obtained results for the two drug candidates from a human taste assessment within Phase I trials, the in-vitro data from the electronic tongue are evaluated in comparison to the outcomes of the taste questionnaires. The retrospective review of the electronic tongue results was performed in the light of in-vivo data in order to discuss the possibilities to predict in future the taste of new entities and drug formulations with electronic tongue studies and take them as guide for formulation development strategies.

2. Materials and methods

2.1. Materials

Samples provided by the company F. Hoffmann-La Roche have been prepared based on the following excipients: the inactive pharmaceutical ingredient (API) CSE3104 (free base, Roche), lactose anhydrous (Supertab 21AN, DFE Pharma, Germany), mannitol (Pearlitol 160C, maltodextrin (Glucidex 17), maltodextrin (Kleptose Linecaps 17) and betadextrin (Kleptose) from Roquette Freres (France), hydroxypropylcellulose LF (Ashland, US), tribasic sodium citrate dihydrate (Jungbunzlauer, Austria), citric acid anhydrous (Merck KGaA, Germany). The standard solution for the e-tongue measurements was prepared based on potassium chloride (Grüssing, Filsum, Germany) and tartaric acid (Appli-Chem, Darmstadt, Germany), the external standard solution was prepared using quinine hydrochloride dihydrate (Buchler GmbH, Germany) and quinine sulfate () was used as model substance; the washing solutions based on ethanol (100%, VWR international, Darmstadt, Germany) and either potassium hydroxide (0.1 M, Grüssing, Filsum) and potassium chloride or aqueous hydrochloric acid (1 M, Merck, Darmstadt, Germany). API CSE3165 (free base, Roche), tribasic sodium citrate dihydrate and citric acid anhydrous (as used for CSE3104), sucralose (Merck KGaA, Germany), sodium benzoate from Emerald Kalama Chemical BV (NL), mannitol (Parteck M100, Roquettes Freres, France), ascorbic acid (DSM Nutritional Products, UK), disodium edetate dihydrate (Titriplex III, Merck Farma, Spain), polyethylenglycol 6000 (Polygykol 6000, Clariant, Germany), tartaric acid (UD Chemie, Germany), strawberry flavor (Givaudan, Switzerland). As summarized in Table 1, properties of the NCEs CSE3104 and CSE3165 are similar to those of quinine.

CSE3165 has a higher potency and requires for this reason significantly lower drug concentrations in solution.

2.2. Electronic taste sensing system

For electronic tongue measurements, the taste sensing system Insent SA402 B (Intelligent Sensor Technology, Inc., Atsugi-chi, Japan) was used. The electronic tongue sensors were purchased from TecLabS (Essen, Germany). They fully met the requirements of the routinely performed sensor checks done by the electronic tongue (Pein et al., 2014; Woertz et al., 2010).

2.3. Measurement procedure of the insent taste sensing system

The taste sensing systems SA402 B is a sensor array system equipped with an Ag/AgCl-reference electrode and a couple of different sensor types. The following sensors were used for the evaluation: SB2AAE: umami taste, SB2CT0: saltiness, SB2CA0: sourness, SB2AE1: astringency, SB2AC0: bitterness (cationic substances), SB2AN0: bitterness (cationic substances), SB2BT0: bitterness (cationic substances), SB2C00: bitterness (anionic substances). Each sample is measured with the electronic tongue four times in a row. The first measurement is excluded from further calculations to avoid any unstable data. Per measurement run 10

Table 1
Characteristics of CSE molecules compared to those of quinine.

molecule	pKs	solubility	M_R [g/mol]
CSE3104	3.1 and 10.9	very good pH dependent solubility in aqueous buffers	<500
CSE3165	4.5 and 6.8	only sufficient and strongly pH dependent solubility at a pH <4	<500
quinine	4.2 and 8.6 (Takács-Novák et al., 1997)	soluble in alkalis and acids (with formation of salts) (Lewis, 2007)	324

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